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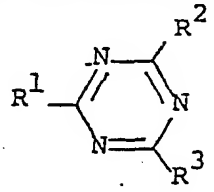
(54) Title: TRIAZINE SYNTHESIS

(57) Abstract

A process for the synthesis of substituted 1, 3, 5-triazine compounds of the general formula:



wherein R^1 and R^2, which may be the same or different, are selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylamino, dialkylamino, arylamino, alkyl-arylamino, alkylthio, arylthio, alkoxy and aryloxy (provided that R^1 and R^2 are not both halogen); and R^3 is selected from the group consisting of halogen, alkylamino, dialkylamino, arylamino, alkyl-arylamino and N-heteroaryl; comprises reaction of a substituted halomethyleneiminium salt with a substituted N-cyanoamidine, N-cyanoguanidine, N-cyanocarbamimidate or N-cyanocarbamidothioate. Substituted 1, 3, 5-triazine compounds having fungal germination inhibition properties are also disclosed. The following compounds 1) 2-chloro-4-phenyl-1, 3, 5-triazine, 2) 2-chloro-4-phenoxymethyl-6-phenyl-1, 3, 5-triazine, 3) 2-N-methylphenylamino-4-phenyl-1, 3, 5-triazine, 4) 2-chloro-4-cyanomethyl-6-phenyl-1, 3, 5-triazine are also disclosed and claimed.

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TRIAZINE SYNTHESIS

This invention relates to a process for the synthesis of 1,3,5-triazine compounds, including in particular mono- or di-alkyl or -aryl substituted 1,3,5-triazines.

1,3,5-Triazines are a class of heterocyclic compounds finding widespread use in many areas of chemical industry - notably as intermediates in plastics manufacture and as herbicides in agriculture. Other triazines are used in disinfectants, algaecides, pharmaceuticals and explosives.

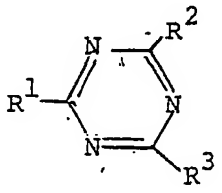
In practice, much of the industrial significance of triazines is confined to the symmetrical triazines including 2,4,6-trihydroxy-s-triazine (cyanuric acid), 2,4,6-triamino-s-triazine (melamine), and 2,4,6-trichloro-s-triazine (cyanuric chloride) and their derivatives, and the chemistry of these compounds has been widely studied, in part because of their ease of synthesis. Despite their intrinsic interest, however, mono- and di-alkyl or -aryl triazines have received relatively little attention. The primary reason for this appears to be the lack of availability of suitable general synthetic methods for this class of triazine derivatives. For example, of the twelve or so methods presently available for the synthesis of this class of triazines few are of preparative value for triazines bearing two alkyl or aryl groups.

N-Cyanoamidines, potentially useful as starting materials for heterocyclic ring formation, have heretofore received scant attention, despite their ready availability from imidates or amidines (K.R.Huffman and F.C.Schaefer, J. Org. Chem., 28, 1812, (1963).), (J.T.Shaw and R.Adams, J. Chem. Eng. Data, 13, 142, (1968).) Their conversion to 1,3,5-triazines by condensation with amides, imidates, amidines and nitriles under a variety of conditions was described by Huffman and Schaefer (supra), but yields were disappointing (15-50%). More recently, low yields of iminodihydrotriazines have been reported (W.Ried and N. Kothe, Chem. Ber., 109, 2706, (1976)) in the reaction of N-cyanoamidines with N-substituted chloroformamidines and imidoyl chlorides, and in one case a 1,3,5-triazine isolated. Attention has now been given to the reaction of N-cyanoamidines, N-cyanoguanidines, N-cyanocarbamimidates or N-cyanocarbamidothioates with halomethyleneiminium salts, leading to the development of a novel synthesis of 1,3,5-triazines which is both versatile and convenient to carry out.

The novel synthesis of triazines from N-cyanoamidines, N-cyanoguanidines, N-cyanocarbamimidates or N-cyanocarbamidothioates and halomethyleneiminium salts in accordance with the present invention is of particular value since it can be successfully applied to the preparation of a wide range of triazine derivatives in which one or two of the substituents is an alkyl or an aryl substituent. Furthermore, by the appropriate choice of starting materials, triazines bearing a hydrogen substituent are also easily available.

The yields are generally high (up to 90%) and the starting materials readily available. The procedures are simple, and the conditions mild and readily amenable to large scale industrial synthesis. The method will, therefore, have wide application, and should open up the scope of triazine chemistry and further the application of triazines in chemical industry.

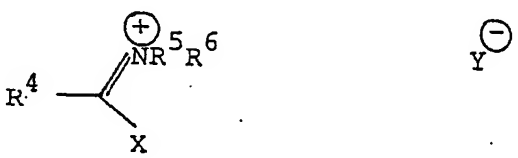
According to the present invention, there is provided a process for the synthesis of substituted 1,3,5-triazine compounds of the general formula I:



I

wherein R^1 and R^2, which may be the same or different, are selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylamino, dialkylamino, arylamino, alkyl-arylamino, alkylthio, arylthio, alkoxy and aryloxy (provided that R^1 and R^2 are not both halogen); and R^3 is selected from the group consisting of halogen, alkylamino, dialkylamino, arylamino, alkyl-arylamino and N-heteroaryl;

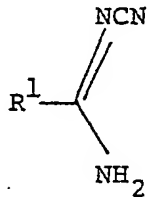
which comprises reaction of a halomethylene-iminium salt of the general formula II:



II

wherein R^4 is selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylthio, arylthio, alkoxy and aryloxy; R^5 and R^6, which may be the same or different, are selected from the group consisting of hydrogen, alkyl and aryl (provided that R^5 and R^6 are not both hydrogen), or R^5 and R^6 together with the nitrogen atom to which they are attached form a saturated heterocyclic ring; X is halogen; and Y is an anion;

with a compound of the general formula III:



III

wherein R^1 is as defined above.

Compounds of the general formula III in which R^1 represents hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl are N-cyanoamidines. Where R^1 represents alkylamino, dialkylamino, arylamino or alkyl-arylamino, the compounds III are N-cyanoguanidines. Similarly, where R^1 represents alkoxy or aryloxy, the compounds III are N-cyanocarbamimidates; and where R^1 represents alkylthio or arylthio, the compounds III are N-cyanocarbamidothioates.

In the above general formulae, the alkyl groups preferably have 1 to 15 carbon atoms (including cycloalkyl groups of 4 to 8 carbon atoms), and suitable aryl groups include phenyl and naphthyl.

Suitable heteroaryl groups include 5 or 6 membered heterocyclic groups having one or more hetero atoms (nitrogen, sulphur or oxygen) and include for example, indolyl and pyrazolyl groups. The substituents which may be present on the alkyl, aryl or heteroaryl groups include one or more substituents selected from the group consisting of halo (particularly chloro or bromo), alkyl (particularly lower alkyl having from 1 to 6 carbon atoms), alkoxy (particularly lower alkoxy having from 1 to 6 carbon atoms), alkylthio (particularly lower alkylthio having from 1 to 6 carbon atoms), aryl (particularly phenyl), aryloxy (particularly phenoxy), arylthio (particularly phenylthio), cyano, nitro, alkoxycarbonyl (particularly lower alkoxycarbonyl), amino and dialkylamino (particularly di (lower alkyl) amino). Halogen groups in the general formulae include bromo and, more preferably, chloro, whilst the anion represented by Y may be a bromide or chloride ion or an inorganic anion such as $OPOCl_2^-$.

The preferred procedure for the synthesis of this invention is to bring together the compounds of formula II and formula III in a suitable inert organic solvent. The following solvents have been found to be suitable: benzene, chloroform, methylene chloride, acetonitrile; the preferred solvent in most reactions being acetonitrile. Alternatively, phosphorus oxychloride may be used in excess as an inorganic solvent.

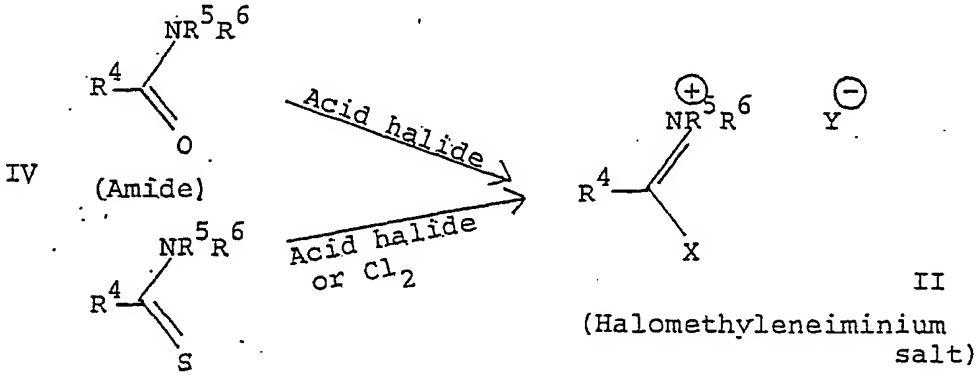
The reaction mixture is then maintained at a suitable temperature (preferably between 0°C and 100°C) for an appropriate length of time (for example, from 15 min. to 6 days), then the 1,3,5-triazine is isolated by precipitation with water or extraction into an organic solvent after addition of water to the reaction mixture. In some cases neutralisation with sodium hydroxide solution is desirable to liberate all the triazine products from their salts. In cases when a mixture of triazines results, separation and purification of the components of the mixture can be effected by chromatography.

As an illustrative example of the process of the present invention, reaction of the chloromethyleneiminium salt (N,N-dimethylbenzamide-$POCl_3$ complex) with N-cyanobenzamidine in acetonitrile at room temperature gives 2-chloro-4, 6-diphenyl-1,3,5-triazine in 70% yield. Extension of the reaction to other chloromethyleneiminium salts, conveniently prepared in situ from N-substituted amides and $POCl_3$ or PCl_5, gives the appropriately substituted 1,3,5-triazine in good yield. Other N-cyanoamidines react analogously, and examples of triazines so prepared are given in Table 1. It is found that in addition to chlorotriazines, small quantities of aminotriazines are sometimes formed, and that these become major products when N-arylamides are used as starting material (see Table 1). These aminotriazines may be formed in a secondary reaction between initially formed chlorotriazines and amines liberated during the cyclisation.

The choice of conditions for the triazine synthesis is governed principally by the reactivity of the amide precursor of the chloromethyleneiminium salt: reactive amides such as dimethylformamide and dimethylacetamide can be reacted with $POCl_3$ in acetonitrile or other inert solvent at room temperature or below whereas unreactive amides such as benzanilide require PCl_5 as the acid chloride component. As previously described in many cases $POCl_3$ can be used in excess as solvent for the reaction.

The N-cyanoamidines used in this synthesis are available by known methods from nitrile precursors via amidine or iminoether intermediates (Huffman and Schaefer, supra, Shaw and Adams, supra). The N-cyanoguanidines, N-cyanocarbamimidates and N-cyanocarbamidiothioates may be prepared by known methods also (E.Grigat and R.Pütter, post.; E.Allenstein, and R.Fuchs, Chem.Ber., 100, 2604 (1967); D.W.Kaiser, and D.Holm-Hansen, U.S.Patent 2697727).

The halomethyleneiminium salts may be prepared by known methods from amide and dithiocarbamate precursors - for a discussion on their preparation, see "Advances in Organic Chemistry", Vol.9, parts 1 and 2 (H. Bohme and H.G. Viehe, editors), "Interscience" (John Wiley and Co., N.Y.), 1976-1979. These methods may be illustrated schematically as follows:



IV (Amide)

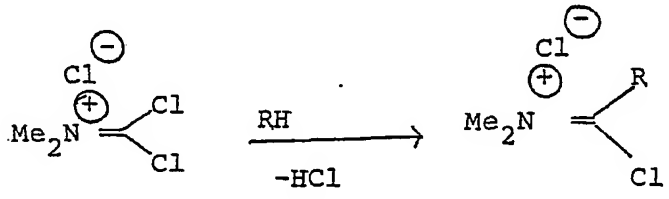
II (Halomethyleneiminium salt)

V (Dithiocarbamate)

It has been found advantageous to prepare many of the halomethyleneiminium salts in situ from the appropriate amide precursor by reaction with an acid halide such as $POCl_3$, PCl_5 or $COCl_2$ in a suitable solvent prior to the addition of the compound of the general formula III. When phosphorus oxychloride is used as the acid halide component it may sometimes be used in excess as solvent for the reaction.

Alkylthiochloromethyleneiminium salts (II, R^4 = alkylthio) may also be prepared in situ from the appropriate dithiocarbamate and phosgene (Eilingsfeld and Mobius, Chem. Ber., 98, 1293, (1965)) and subsequently reacted with a compound of the general formula III in acetonitrile or phosphorus oxychloride as solvent.

Dichloromethyleneiminium salts may be generated from S,N,N-trialkyldithiocarbamates by reaction with chlorine. It is known that dichloromethyleneiminium salts may be reacted with activated aromatic or heterocyclic compounds, phenols or thiophenols to produce other reactive methyleneiminium salts in which one of the chlorines is displaced by an aryl, heteroaryl, aryloxy or arylthio group. This is shown schematically below, using dichloromethylenedimethyliminium chloride as example:



VI

(see "Advances in Organic Chemistry" Vol.9 Parts 1 and 2, supra).

The derived reagents VI are of course chloromethyleneiminium salts of the class II described earlier and may be generated in situ and used in the new triazine synthesis as described above. By way of example, reaction of dichloromethylenedimethyliminium chloride with one equivalent of N,N-dimethylaniline for 15 min. in acetonitrile at reflux generates reagent VI where R = P-dimethylaminophenyl. Addition of N-cyanobenzamidine and further reflux gives, after work-up, 2-(p-dimethylaminophenyl) -4-phenyl-6-chloro-1,3,5-triazine. Similarly, reaction of dichloromethylenedimethyliminium chloride with one equivalent of phenol in methylene chloride generates reagent VI where R = phenoxy, and further reaction with cyanobenzamidine gives 2-chloro-4-phenoxy-6-phenyl-1,3,5-triazine.

The reaction of the present invention therefore represents a facile route to diversely substituted 1,3,5-triazines, many of which are not otherwise readily accessible. In addition, the novel synthesis enables access to certain compounds of the general formula I above which are themselves novel.

Table 1 hereinafter illustrates the preparation of a number of different substituted 1,3,5-triazine compounds in accordance with this invention:

TABLE 1

Chloromethylene-iminium salt R^4	R^5	R^6	Y	N-cyano-amidine[c] R^1	Solvent/ Conditions	1,3,5-Triazine I	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Molecular formula[a] or Lit.m.p.	Mass Spectrum[b]
Ph	Me	Me	$OPOCl_2$	Ph	MeCN/½h reflux	a	Ph	Ph	Cl	70	139	138-9	267
H	Me	Me	$OPOCl_2$	Ph	MeCN/15 min. 25°	b	Ph	H	Cl	56	86-87	$C_9H_6ClN_3$ (191.6)	191
Me	Me	Me	$OPOCl_2$	Ph	C_6H_6/18h 25°	c	Ph	Me	Cl	81	75	75.5-76.5	205
						d	Ph	Me	NMe_2	5	63	$C_{12}H_{14}N_4$ (214.3)	214
Me	H	Ph	$OPOCl_2$	Ph	MeCN/1 h reflux	c	Ph	Me	Cl	4	75		
						e	Ph	Me	NHPh	84	133	$C_{16}H_{14}N_4$ (262.3)	262
Ph	H	Ph	Cl	Ph	MeCN/1 h reflux	a	Ph	Ph	Cl	48	139		
						f	Ph	Ph	NHPh	25	155	155	324
Indol-3-yl	Me	Me	$OPOCl_2$	Ph	MeCN/6 days 25°	g	Ph	Indol-3-yl	Cl	47	195	$C_{17}H_{11}ClN_4$ (306.75)	306
Cl	Me	Me	Cl	Ph	$POCl_3$/15 min. reflux	h	Ph	Me_2N	Cl	85	105	$C_{11}H_{11}ClN_4$ (234.7)	234
MeS	Me	Me	Cl	Ph	$POCl_3$/½ h reflux	i	Ph	MeS	Cl	56	89	$C_{10}H_8ClN_3S$ (237.7)	237
Ph	Me	Me	$OPOCl_2$	Me	MeCN/½h reflux	c	Me	Ph	Cl	49	75		
						d	Me	Ph	NMe_2	5	63		

TABLE 1 (cont'd)

Chloromethylene-iminium salt R^4	R^5	R^6	Y	N-cyano-amidine[c] R^1	Solvent/ Conditions	1,3,5-Triazine I	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Molecular formula[a] or Lit.m.p.	Mass Spectrum[b]
Ph	Me	Me	$OPOCl_2$	$ClCH_2$	MeCN/1 h reflux	j	$ClCH_2Ph$		Cl	88	86-87	$C_{10}H_7Cl_2N_2$ (240.1)	239
Ph_2CH	$-(CH_2)_4-$		Cl	Ph	MeCN/48h reflux	k	Ph	Ph_2CH	$N(CH_2)_4$	64	183-184	$C_{26}H_{24}N_4$ (392.48)	392
$PhOCH_2$	Et	Et	$OPOCl_2$	Ph	MeCN/½h reflux	l	Ph	$PhOCH_2$	Cl	67	81	$C_{16}H_{12}ClN_3O$ (297.74)	297
oToluyl	Me	Me	$OPOCl_2$	Ph	$POCl_3$/1h reflux	m	Ph	oToluyl	Cl	80	72-7	$C_{16}H_{12}N_3Cl$ (281.74)	281
$CH_3(CH_2)_{10}$	H	cyclo-hexyl	$OPOCl_2$	Ph	MeCN/½h reflux	n	Ph	$CH_3(CH_2)_{10}$	Cl	87	44-5	$C_{20}H_{28}ClN_3$ (345.5)	345
$PhCH_2$	Me	Me	$OPOCl_2$	Ph	MeCN/½h reflux	o	Ph	$PhCH_2$	Cl	14	oil	$C_{16}H_{12}ClN_3$ (281.74)	281
H	Me	Ph	$OPOCl_2$	Ph	MeCN/½h reflux	p	Ph	H	N(Me)Ph	67	80	$C_{16}H_{14}N_4$ (262.30)	262
Me_2N-	Me	Me	Cl	Ph	MeCN/1½h reflux	q	Ph	Me_2N-	Cl	35		$C_{17}H_{15}ClN_4$ (310.5)	310
$EtCOOCH_2$	H	cyclo-hexyl	$OPOCl_2$	Ph	MeCN/1h reflux	r	Ph	$EtOOCCH_2$	Cl	60		$C_{13}H_{12}ClN_3O_2$ (277.5)	277

TABLE 1 (cont'd)

Chloromethylene-iminium salt R^4	R^5	R^6	Y	N-cyano-amidine[c] R^1	Solvent/ Conditions	1,3,5-Triazine I	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Molecular formula[a] or Lit.m.p.	Mass Spectrum[b]
PhO	Me	Me	Cl	Ph	CH_2Cl_2/2h reflux	s	Ph	PhO	Cl	53	103	$C_{15}H_{10}ClN_3O$ (283.71)	283
Ph	Me	Me	$OPOCl_2$	PhO	MeCN/1h reflux	s	PhO	Ph	Cl	71	103	$C_{15}H_{10}ClN_3O$ (283.71)	283
	$-(CH_2)_4-$		$OPOCl_2$	MeS	MeCN/1h reflux	t	MeS		Cl	62	92-3	$C_8H_6ClN_3OS$ (227.61)	227
$pMeC_6H_4$	Me	Me	$OPOCl_2$	EtO	MeCN/½h reflux	u	EtO	$pMeC_6H_4$	Cl	80	78	$C_{12}H_{12}ClN_3O$ (249.70)	249
Ph	Me	Me	$OPOCl_2$	Cl	CH_2Cl_2/18h Rm. Temp.	v	Cl	Ph	Cl	58	118-9	119-120	
Ph	Me	Me	Br	Ph	CH_2Cl_2/18h Rm. Temp.	w	Ph	Ph	Br	58	115	$C_{15}H_{10}BrN_3$ (312.17)	311
Ph	Me	Me	Cl	COOEt	CH_2Cl_2/18h Rm. Temp.	x	COOEt	Ph	Cl	41	70-71	$C_{12}H_{19}ClN_3O_2$ (263.5)	263

a. Microanalyses were in satisfactory agreement with calculated values (maximum deviation C ± 0.42, H ± 0.27, N ± 0.32).

b. Mass spectra recorded on A.E.I. MS-9 instrument; molecular ions containing ^{35}Cl or ^{79}Br are shown.

c. Or related compounds. See supra.

1,3,5-triazines which can be prepared in accordance with the present invention have been found to exhibit fungal germination inhibition properties as shown in Table 2.

TABLE 2

Inhibition of Germination of Tilletea Foetida by 1,3,5-Triazines

1,3,5-Triazines	Spore Germination inhibition at 10 ppm (%)
2-chloro-4-phenyl	100
2-chloro-4-phenoxymethyl-6-phenyl	100
2-N-methylphenylamino-4-phenyl	100
2-chloro-4-cyanomethyl-6-phenyl	100

The process of the present invention is further illustrated by the following specific examples:

EXAMPLE 1

2-Chloro-4, 6-diphenyl-1,3,5-triazine (Ia):

N,N-Dimethylbenzamide (1.49 g, 10 mmol), is heated with $POCl_3$ (1 ml) on a steam bath at 100° for 5 min. The resulting complex is dissolved in acetonitrile (10 ml) and a solution of N-cyanobenzamidine (1.45 g, 10 mmol) in acetonitrile (20 ml) is added. After several minutes the triazine begins to separate; after 30 min water is added to complete the precipitation and the product is collected, washed with water and recrystallized from ethanol-water; yield: 1.8 g (70%); m.p. 139° (lit., 138-9°).

EXAMPLE 2

2-Anilino-4-methyl-6-phenyl-1,3,5-triazine (Ie):

N-Cyanobenzamidine (1.45 g, 10 mmol), acetanilide (1.35 g, 10 mmol) and $POCl_3$ (1 ml) are refluxed in acetonitrile (20 ml) for 1 h. The hydrochloride of (Ie) precipitates as a pale yellow crystalline solid, m.p. 198-204°, and is collected after the mixture has been allowed to stand at room temperature over night (yield 2.5 g, 84%). The free triazine is obtained as colorless flat needles, m.p. 133° and is identical (m.p., mixed m.p., nmr, ir and mass spectrum) with samples prepared by reaction of (Ic) with aniline in acetonitrile (reflux, 30 min) and from the reaction of N-phenylbenzimidoyl chloride and N-cyanoacetamidine according to Ried and Kothe (Chem. Ber., 109, 2706, (1976).) The benzene-soluble fraction from the reaction mixture is washed with dilute ammonia, dried ($MgSO_4$) and chromatographed on silica gel (Merck 70-30 mesh ASTM) eluting with benzene. The first fractions from the column contain (Ic) (0.075 g, 3.7%), m.p. 75° (Lit. 75.5-76.5°).

EXAMPLE 3

2-Chloro-4-phenyl-6-methylthio-1,3,5-triazine (Ii):

S,N,N-Trimethyldithiocarbamate (1.35 g, 10 mmol) is dissolved in toluene (10 ml) containing phosgene (20%, w/v) and the solution kept at room temperature protected from moisture for 1 hr. The solvent and excess phosgene are evaporated in vacuo and to the residue is added $POCl_3$ (10 ml) and N-cyanobenzamidine (1.45 g). The mixture is refluxed for 30 min and poured into water. The product is extracted into benzene and purified by chromatography on silica gel eluting with benzene; the first fractions contain the methylthiotriazine (Ii) (1.3 g, 56%), m.p. 89°.

EXAMPLE 4

2-chloro-4-phenyl-6-(p-dimethylaminophenyl)-1,3,5-triazine (Iq):

Dichloromethylene dimethyliminium chloride (1.9g) was suspended in acetonitrile (20 ml) and N,N-dimethylaniline (1.3 ml) added. The mixture was refluxed until all solids had dissolved (15 min.) then N-cyanobenzamidine (1.45g) added. The mixture was refluxed a further 1½h and poured into water. An orange solid precipitated and after adjusting the pH to 5 with solid sodium acetate the mixture was allowed to stand at room temperature overnight. The solid was collected and recrystallised from ethanol to give the dimethylaminophenyltriazine (1.1g 35%) as orange needles, m.p. 169-70°.

EXAMPLE 5

2-chloro-4-phenyl-6-undecyl-1,3,5-triazine (In):

N-cyclohexyl dodecanamide (1.4g), phosphorous oxychloride (0.5 ml) and N-cyanobenzamidine (0.80g) were heated under reflux in acetonitrile (20 ml) for ½h. The mixture was poured into water and the solid collected. The product was purified by passage of its solution in methylene chloride through a short column of silica gel; removal of the solvent from the eluate gave a pale tan oil which crystallised. Yield 1.5 g 87%, m.p. 44-45°.

EXAMPLE 6

2-chloro-4-phenoxy -6- phenyl-1,3,5-triazine (Is):

METHOD A: Dichloromethylenedimethyliminium chloride (1.8g) was added to a stirred solution of phenol (1g) in dry dichloromethane (50 ml). After 15 min a clear solution had resulted, to which was added N-cyanobenzamidine (1.45g).

The mixture was heated under reflux protected from moisture for 2 h, the solvent evaporated and the residue recrystallised from aqueous ethanol giving the phenoxy-triazine (Is) as colorless plates (1.8g, 53%), m.p. 103°.

METHOD B: Phosphorous oxychloride (0.4 ml) was added to N,N-dimethylbenzamide (0.6 g) dissolved in acetonitrile (10 ml). After 15 min at room temperature, N-cyano-O-phenylcarbamimidate (E.Grigat and R.Putter Chem. Ber., 98, 2619, (1965)) (0.65 g) was added and the mixture heated under reflux protected from moisture for 1 h. Water (100 ml) was added and the precipitate collected after 1 h and recrystallised from aqueous ethanol. The phenoxy-triazine (0.8 g, 71%) had m.p. 103° and was identical (nmr, mass spec, mixed m.p.) to that obtained by method A.

EXAMPLE 7

2-chloro-4(2[1]-furyl)-6-methylthio-1,3,5-triazine (It):

Phosphorous oxychloride (1 ml) was added to a solution of 2-furfuroylpyrrolidine (1.65 g) in acetonitrile (20 ml). After 15 min N-cyano-S-methylcarbamimidothioate (R.W.Turner, Synthesis, (1975), 332) (1.2 g) was added and the mixture heated under reflux protected from moisture for 1 h and then poured into water (100 ml). The precipitate was collected after 1 h and recrystallised from petroleum ether (bp 60-80°) to give the methylthiotriazine (It) as colorless needles (1.4 g, 62%), m.p. 92-93°.

EXAMPLE 8

2-chloro-4-ethoxy-6-p-tolyl-1,3,5-triazine (Iu):

N,N-dimethyl-p-toluamide (1.65 g) and phosphorous oxychloride (1 ml) were dissolved in acetonitrile (20 ml). To the solution was added N-cyano-O-ethyl carbamimidate (1.13 g) and the mixture heated under reflux protected from moisture for ½ h. Water (100 ml) was added and the precipitated product collected after 1 h at 0 °C and recrystallised from aqueous ethanol to give the ethoxy-triazine (Iu) as colorless needles (2 g, 80%), m.p. 78°.

EXAMPLE 9

2,4-Dichloro-6-phenyl-1,3,5-triazine (Iv):

N,N-Dimethylbenzamide (1.5 g) and phosphorous oxychloride (1 ml) were dissolved in methylene chloride (20 ml) and the mixture kept at room temperature for 15 min. N-Cyanochloroformamidine (1.1 g) (E. Allenstein, Z. Anorg. Allgem. Chem., 322, 265 (1963)) was added and the mixture stirred at room temperature overnight protected from moisture. The mixture was shaken with water (100 ml) and the organic phase separated, dried, concentrated in vacuo and applied to a column of silica gel (2 x 15 cm). Elution with benzene gave the dichloro-triazine (1.3 g, 58%) which crystallised from ethanol as colorless needles, m.p. 118-119° (lit 120°).

EXAMPLE 10

2-Bromo-4,6-diphenyl-1,3,5-triazine (Iw):

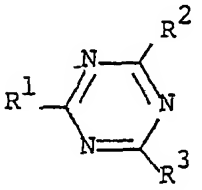
N,N-Dimethylbenzamide (1.5 g) was added to a stirred solution of phosphorous tribromide (2 ml) and bromine (1 ml) in methylene chloride (50 ml) and the mixture stirred protected from moisture at room temperature for 1 h. Cyclohexene (2 ml) was added to discharge the

bromine colour, followed by N-cyanobenzamidine (1.45 g). The mixture was protected from moisture and stirred overnight. Water (100 ml) was added and stirring continued for 5 min. The organic layer was separated, dried and the solvent removed in vacuo. The product was purified by passage of its solution in methylene chloride through a short column of silica gel. Evaporation of the eluate and recrystallisation of the residue from ethanol gave the bromotriazine (Iw) as colorless fine needles (1.75 g, 58%), m.p. 155°.

It will be appreciated by those skilled in the art that modifications and variations may be made to the specific details included herein without departing from the broad teaching of the present invention and the invention thus encompasses all such modifications and variations.

CLAIMS:

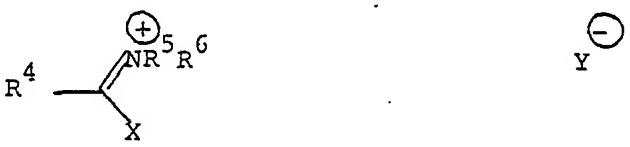
1. A process for the synthesis of substituted 1,3,5-triazine compounds of the general formula I:



I

wherein R^1 and R^2, which may be the same or different, are selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylamino, dialkylamino, arylamino, alkyl-arylamino, alkylthio, arylthio, alkoxy and aryloxy (provided that R^1 and R^2 are not both halogen); and R^3 is selected from the group consisting of halogen, alkylamino, dialkylamino, arylamino, alkyl-arylamino and N-heteroaryl;

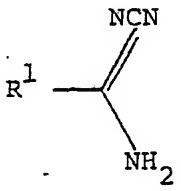
which comprises reaction of a halomethylene-iminium salt of the general formula II:



II

wherein R^4 is selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylthio, arylthio, alkoxy and aryloxy; R^5 and R^6, which may be the same or different, are selected from the group consisting of hydrogen, alkyl and aryl (provided that R^5 and R^6 are not both hydrogen), or R^5 and R^6 together with the nitrogen atom to which they are attached form a saturated heterocyclic ring; X is halogen; and Y is an anion;

with a compound of the general formula III:



III

wherein R^1 is as defined above.

2. A process according to claim 1, wherein said reaction is carried out in an inert organic solvent.

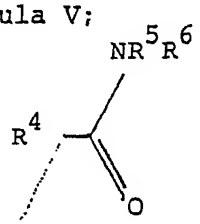
3. A process according to claim 2, wherein said inert organic solvent is selected from the group consisting of acetonitrile, benzene, chloroform and methylene chloride.

4. A process according to claim 1, wherein said reaction is carried out in an excess of phosphorus oxychloride as an inorganic solvent.

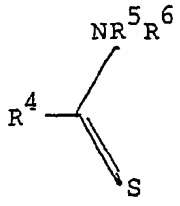
5. A process according to any one of claims 1 to 4, wherein said substituted 1,3,5-triazine compounds are isolated from the reaction mixture by precipitation with water or by extraction into an organic solvent after addition of water.

6. A process according to claim 5, wherein said reaction mixture is neutralised prior to extraction of said substituted 1,3,5-triazine compounds.

7. A process according to any one of claims 1 to 6, wherein said halomethyleneiminium salt of the general formula II is prepared by reaction of an amide of the general formula IV; or a dithiocarbamate of the general formula V;



IV



V

wherein R^4, R^5 and R^6 are as defined in claim 1, with an acid halide.

8. A process according to claim 7, wherein said acid halide is selected from $POCl_3$, $POCl_5$ or $COCl_2$.

9. A process according to claim 8, wherein said halomethyleneiminium salt is prepared in situ by reaction of an amide of the general formula IV as defined in claim 7 with phosphorus oxychloride, said phosphorus oxychloride being used in excess as solvent for the reaction.

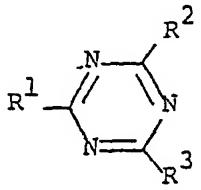
10. A process according to claim 1, substantially as herein described with reference to Table 1 or in any one of Examples 1 to 10.

11. Substituted 1,3,5-triazine compounds of the general formula I as defined in claim 1, whenever prepared by a process according to any one of claims 1 to 10.

12. A substituted 1,3,5-triazine compound selected from the group consisting of 2-chloro-4-phenyl-1,3,5-triazine, 2-chloro-4-phenoxymethyl-6-phenyl-1,3,5-triazine, 2-N-methylphenylamino-4-phenyl-1,3,5-traizine and 2-chloro-4-cyanomethyl-6-phenyl-1,3,5-triazine.

AMENDED CLAIMS
(received by the International Bureau on 20 August 1981 (20.08.81))

1. A process for the synthesis of substituted 1,3,5-triazine compounds of the general formula I:



I

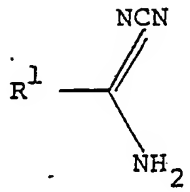
wherein R^1 and R^2, which may be the same or different, are selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylamino, dialkylamino, arylamino, alkyl-arylamino, alkylthio, arylthio, alkoxy and aryloxy (provided that R^1 and R^2 are not both halogen); and R^3 is selected from the group consisting of halogen, alkylamino, dialkylamino, arylamino, alkyl-arylamino and N-heteroaryl;

which comprises reaction of a halomethylene-iminium salt of the general formula II:

II

wherein R^4 is selected from the group consisting of hydrogen, halogen, alkoxycarbonyl, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylthio, arylthio, alkoxy and aryloxy; R^5 and R^6, which may be the same or different, are selected from the group consisting of hydrogen, alkyl and aryl (provided that R^5 and R^6 are not both hydrogen), or R^5 and R^6 together with the nitrogen atom to which they are attached form a saturated heterocyclic ring; X is halogen; and Y is an anion;

with a compound of the general formula III:



III

wherein R^1 is as defined above.

2. A process according to claim 1, wherein said reaction is carried out in an inert organic solvent.

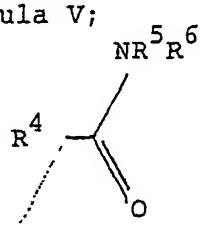
3. A process according to claim 2, wherein said inert organic solvent is selected from the group consisting of acetonitrile, benzene, chloroform and methylene chloride.

4. A process according to claim 1, wherein said reaction is carried out in an excess of phosphorus oxychloride as an inorganic solvent.

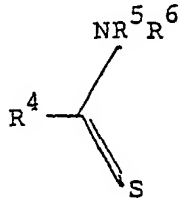
5. A process according to any one of claims 1 to 4, wherein said substituted 1,3,5-triazine compounds are isolated from the reaction mixture by precipitation with water or by extraction into an organic solvent after addition of water.

6. A process according to claim 5, wherein said reaction mixture is neutralised prior to extraction of said substituted 1,3,5-triazine compounds.

7. A process according to any one of claims 1 to 6, wherein said halomethyleneiminium salt of the general formula II is prepared by reaction of an amide of the general formula IV; or a dithiocarbamate of the general formula V;



IV



V

wherein R^4, R^5 and R^6 are as defined in claim 1, with an acid halide.

8. A process according to claim 7, wherein said acid halide is selected from $POCl_3$, $POCl_5$ or $COCl_2$.

9. A process according to claim 8, wherein said halomethyleneiminium salt is prepared in situ by reaction of an amide of the general formula IV as defined in claim 7 with phosphorus oxychloride, said phosphorus oxychloride being used in excess as solvent for the reaction.

10. A process according to claim 1, substantially as herein described with reference to Table 1 or in any one of Examples 1 to 10.

11. Substituted 1,3,5-triazine compounds of the general formula I as defined in claim 1, whenever prepared by a process according to any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 81/00046

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[3] C07D 251/16, 251/22, 405/04, 403/04

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC	C07D 251/16, 251/22, 405/04, 403/04
US Cl.	544-187,-188,-189,-190,-194,-196,-197,-198,-199,-204,-205,-206,-207,-208,-209,-210,-211,-212,-213,-215,-216,-217,-218,-219.

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

AU: IPC as above; Australian Classification 09.62-41

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
P,X	Australian Journal of Chemistry, Vol. 34, No. 3, issued 1981, March (CSIRO, Melbourne), R. Harris, "The Synthesis of Alkyl- and Aryl-Substituted 1,3,5,-Triazines", see pages 623-34	1-12
X	Chemische Berichte, Vol. 109, issued 1976, Reid et al, "Uber Umsetzungen von Chlorformamidinen und N-Phenyl-benzimidoylchlorid mit N-Cyanamidinen und 1-Cyanguanidin", see pages 2706 to 2715.	1
A	US, A, 3203550, published 1965, August 31, Schaefer.	1
A	US, A, 3154547, published 1964, October 27, Huffman	1
A	DE, A, 1178437, published 1964, September 24, Farbenfabriken Bayer AG.	1
A	Journal of Heterocyclic Chemistry, Vol. 7, issued 1970, August, Crenshaw et al. "A Synthesis of Isothiazoles and Pyrimidines via a Vilsmeier - Haack Reaction", see pages 871 to 873.	

* Special categories of cited documents: [15]

"A" document defining the general state of the art

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
29 June 1981 (29.06.81)	03 July 1981 (03-07-81)
International Searching Authority [1]	Signature of Authorized Officer [20]
AUSTRALIAN PATENT OFFICE	A.S. Moore. A A Moore

Form PCT/ISA/210 (second sheet) (October 1977)